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Systematic Review and Meta-analysis of Randomized Controlled Trials evaluating prophylactic intra-operative wound irrigation for the prevention of surgical site infections

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Abstract

Background: Surgical site infections (SSIs) are one of the most common hospital acquired infections. To reduce SSIs prophylactic intraoperative wound irrigation (pIOWI) has been advocated, although results are equivocal. To develop recommendations for the new World Health Organization (WHO) SSI prevention guidelines, a systematic literature review and a meta-analysis were conducted on the effectiveness of pIOWI using different agents to reduce SSI.

Methods: Pubmed, Embase, CENTRAL, CINAHL, and WHO databases were searched. Randomized controlled trials (RCTs) comparing either pIOWI *to* no pIOWI, or *to* pIOWI using different solutions and techniques, were included with SSI as the primary outcome. Meta-analyses were performed and odds ratios (OR) and the mean difference with 95% confidence intervals (CI) were extracted and pooled with a random effects model.

Results: Twenty-one studies were available and a distinction was made between intraperitoneal, mediastinal and incisional wound irrigation. Low quality of evidence demonstrated a statistically significant benefit for incisional wound irrigation with an aqueous povidone iodine (PVP-I) solution in clean and clean contaminated wounds (OR 0.31 (95% CI: 0.13-0.73), p=0.007; 50 fewer SSIs per 1.000 procedures (from 19 fewer to 64 fewer)). Antibiotic irrigation had no significant effect in reducing SSIs (OR 1.16 (95% CI: 0.64-2.12, p=.63).

Conclusion: Low quality evidence suggests considering the use of prophylactic incisional wound irrigation to prevent SSI with an aqueous povidone iodine solution. Antibiotic wound irrigation does not show a benefit and is therefore discouraged.

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Introduction

Surgical site infections (SSIs) are an adverse outcome of surgery accounting for the majority of healthcare associated infections around the world (1-3). In developing countries, more than one in ten of all surgical procedures is complicated by a SSI (2). Although the overall risk of SSIs is much lower in developed countries, they remain a serious threat to patient safety (1, 3). SSIs cause increased morbidity, mortality and prolonged hospital stay (1, 4, 5). The average SSI is associated with approximately one additional week of hospitalization and increases mortality risk 2- to 11-fold as compared to uninfected surgical patients (5). Moreover, SSIs increase healthcare costs in the US up to $1.6 billion per year (4). Many factors have been associated with the risk of SSI and consequently a range of preventive measures has been proposed. One of these preventive measures is prophylactic intraoperative wound irrigation (pIOWI), a seemingly simple intervention defined by the flow of a solution across the surface of an open wound to achieve wound hydration. It physically removes and dilutes body fluids, bacteria and cellular debris and additionally may have a bactericidal effect when additives as antibiotics or antiseptic agents are used (see table 1 for an overview of definitions used). Up to 97% of the surgeons commonly practice IOWI (6, 7). Nonetheless, it is not part of general practice in every country or hospital. Moreover, methods vary depending on the patient population, surface of application, technique and solutions used. Similar variations in methodology and results can be observed in studies investigating the effect of IOWI (8).

Among the available guidelines on SSI prevention, few have addressed the topic of IOWI and give contradictive recommendations. The guidelines by the United

Kingdom National Institute for Health and Care Excellence (NICE) issued in 2008, updated in 2013, advised against IOWI and intraperitoneal lavage (9). In contrast, the 2014 guidelines of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend using antiseptic wound lavage (10). Many of the solutions commonly used for irrigation are not licensed for open wounds by the United States (US) Food and Drug Administration (11).

In 2015 a meta-analysis has been published to determine the current state of knowledge on pIOWI (8). However, that review does not take into account that (other) infection prevention measures among included studies have improved over decades. Therefore, the presented evidence may not be generalizable to current standard of care (i.e., no appropriate standard systemic antibiotic prophylaxis). Importantly, the previous review has included studies where pIOWI represents a therapeutic intervention for infection rather than a prophylactic measure. Also, a substantial heterogeneity between studies has not been accounted for as the previous review does not account for differences in irrigation solutions and in application methods. For the purpose of developing recommendations for the new World Health Organization (WHO) SSI prevention guidelines (12, 13), a systematic literature review and meta-analysis were conducted. In present systematic review we aim to assess all available data reasonably applicable to current standard of care and clarify the effect of pIOWI on the incidence of surgical site infection in all surgical populations, while accounting for inter-study differences in application method and solution.

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Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (14).

Search strategy and selection criteria

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. No time limit was used because most studies were published before 1990. Language was restricted to English, French, German and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MESH), the complete search is included in appendix A.

Two independent reviewers screened titles and abstracts of retrieved references for potentially relevant studies. The full text of these articles was obtained and independently reviewed for eligibility based on inclusion criteria. Duplicate studies were excluded. Only randomized studies investigating pIOWI as described in Table 1 were included. Studies investigating the topical application of antibiotics and antiseptics (e.g., powder, gels, sponges) without the mechanical effect of irrigation, physically rinsing and diluting the bacterial load, were not included. To ensure that only evidence reasonably relevant to the current standard of care was included in our analyses, description of appropriate administration of preoperative antibiotic prophylaxis (i.e., before incision and intravenous) was a minimum requirement for inclusion. In addition, studies where the irrigated field was infected prior to the start of surgery and wound irrigation, represented a therapeutic intervention rather than

a prophylactic measure and were also excluded. Wound contamination was ranked according to the US Centers for Disease Control and Prevention (CDC) wound classification(15). As described in table 1, wound class I-III were considered not infected and therefore irrigation of the contaminated field a prophylactic measure, whereas CDC Wound class IV was considered a pre-existent infection and therefore irrigation of the contaminated field represented a therapeutic intervention. Irrigation of the newly made incisional wound was always considered prophylactic, regardless of the wound classification, as the incisional wound did not exist prior to the procedure and pre-existent infection would be impossible. For example, peritoneal cavity irrigation of a dirty, infected abdomen (CDC Wound class IV) represents a therapeutic intervention. In contrast, in the same procedure incisional wound irrigation was considered a prophylactic measure.

Data extraction and assessment of study quality

Data were extracted from the text, according to a pre specified data abstraction form including design, publication date, scope, number of patients, contamination according to the US CDC wound classification (15), irrigation surface, type of intervention (solution, application, volume), type of control, Follow-up, primary outcome, results and adverse events (AE) (appendix B). The Cochrane Collaboration's tool(16) for assessing risk of bias was assessed for the quality of the studies. Any disagreements were resolved through discussion or after consultation with the senior author, when necessary. Publication bias was assessed using a funnel plot (17). The Grading of Recommendations Assessment, Development and Evaluation

(GRADE) methodology (GRADE Pro software, http://gradepro.org/) (18) was used to assess the quality of the body of retrieved evidence.

Synthesis of results

Trials were grouped in comparisons according to irrigation location and their intervention and control arm. Of each comparison meta-analysis were performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) as appropriate. If only one study no data could be pooled, but data were plotted as forest plot for illustrative purposes. Odds ratios (OR) and the mean difference with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model (Mantel-Haenszel method) to account for potential heterogeneity (19). Forest plots were constructed and $P< 0.05$ was considered to be statistically significant. Heterogeneity was assessed using the I^2 statistic. I^2 of >60% was assessed as serious inconsistency. When inconsistency was detected stratified subgroup analysis where made for wound contamination and for irrigation solution.

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Results

Study selection

We identified 955 studies. Hundred thirteen were assessed for full review. Twenty-one randomized controlled trials (RCTs) were found eligible for full critical appraisal. The process of selection is summarized in Figure 1. Reasons for exclusion after full text assessment are described in appendix C.

Study characteristics

In total we identified 21 RCTs (20-40) (6224 patients) comparing pIOWI to no pIOWI or to pIOWI using different solutions and techniques, in patients undergoing various surgical procedures with SSI as an outcome. All but two (27, 28) were single center RCTs. There was substantial heterogeneity in the study protocols. A distinction was made between peritoneal cavity, mediastinal cavity and incisional wound irrigation. Other main differences were the composition of the irrigation fluid, and the type of surgery with associated contamination. Due to this heterogeneity of the evidence, nine separate comparisons were composed. Five studies describing intraoperative peritoneal cavity irrigation (20-24) comparing *saline solution vs. no irrigation (20)*, *taurolidine vs. saline solution (21)* and *antibiotic irrigation vs saline or no irrigation (22-24);* fifteen describing incisional wound irrigation (25-39) comparing *saline solution vs. no irrigation (25)*, *syringe pressure irrigation with saline solution vs. no irrigation (26)*, *pulse pressure irrigation with saline solution vs. normal saline solution (27, 28)*, *aqueous* povidone iodine *(PVP-I) vs. saline solution (29-35) and antibiotic vs. saline solution or no irrigation (22, 36-39);* and one study describing intraoperative mediastinal cavity irrigation (40) comparing *aqueous PVP-I vs. saline solution.* Most

studies were conducted in patients undergoing abdominal surgery (20-24, 26, 28, 31, 32, 36, 37) but spine (33, 34), orthopedic (27, 35, 39), gynecologic (25), vascular (38), thoracic (40) and general surgery (29, 30) were also included. Of the included studies 3 RCTs (20, 23, 31) described sterility of the irrigation fluid. The other studies did not report whether the irrigation fluid was sterile or not. The evidence table with study characteristics is summarized in Table 2 and entirely presented in Appendix B.

Risk of bias

The results of the risk of bias evaluation are presented in Table 3. Overall there was serious risk of bias, predominantly due to unclear or high risk of selection and performance bias. Publication bias could not be detected or excluded. There was an insufficient number of studies included in the separate meta-analyses for appropriate interpretation of the funnel plots.

Data and analyses

A summary of the evidence is presented in Table 4. For an extensive overview of all nine comparisons, corresponding data and meta-analyses we refer to appendix D.

No effective strategy for the reduction of SSIs with prophylactic peritoneal cavity irrigation was identified.

Regarding incisional wound irrigation, mere saline irrigation was not effective in reducing SSIs (25). However, when the saline solution was applied with a syringe to generate some pressure (26) a reduction in the risk of SSI compared to no irrigation was shown in one study (OR 0.35 (95% CI: 0.19-0.65); P=0.0009). This benefit was also demonstrated when pulse pressure irrigation with saline was compared with

normal saline irrigation in a meta-analysis of two RCTs (27, 28) (OR 0.30 (95% CI: 0.08-0.86); p=0.0003).

Irrigation with aqueous povidone iodine demonstrated a significant benefit when compared with saline solution irrigation in a meta-analysis of 7 RCTs (29-35) (OR 0.31 (95% CI: 0.13-0.73); p=0.007; Figure 2a-c). This effect equals 50 fewer SSIs per 1.000 procedures (from 19 fewer to 64 fewer) (appendices D and E comparison 7). The results where stratified according to subgroups based on wound contamination (Figure 2b) and povidone iodine concentration (Figure 2c) to account for heterogeneity in the pooled analysis (I^2=63%). Thereby, heterogeneity decreased to an I^2 of 43 %. The effect of irrigation with aqueous povidone iodine on SSIs was attributable to incisional wound irrigation in clean and clean-contaminated procedures with PVP-I 10% and PVP-I 0.35%. No dose response effect was seen.

Antibiotic irrigation of the incisional wound showed no effect on SSI rate compared to no irrigation or saline irrigation in a meta-analysis of five RCTs (22, 36-39) (OR 1.16 95% CI: 0.64-2.12 p=0.63) (Figure 3). This lack of effect equals 12 more SSIs per 1.000 (from 27 fewer to 76 more) (appendices D and E comparison 8).

Only one study reported on mediastinal irrigation with aqueous povidone iodine compared to normal saline irrigation and showed no benefit (40) .

Adverse events

Among the included studies, six studies (29, 31, 33, 34, 36, 41) reported no adverse events attributable to the intervention. Among these, two studies (33, 34) investigating PVP-I wound irrigation in spinal surgery specifically reported no difference in fusion time or bone quality. One study (31) investigating PVP-I wound

irrigation in abdominal surgery specifically reports transient serum iodine elevation to a nine fold (median: 162 mcg/dl, range 27-1170 mcg/dl), but no clinical signs of toxicity. After seven days, serum iodine levels returned to pre-operative ranges.

GRADE

GRADE tables with full assessment of the individual comparisons are presented in appendix E. Overall the quality of evidence was assessed as moderate to very low due to the serious risk of bias and serious imprecision.

Discussion

Low quality evidence shows that prophylactic incisional wound irrigation with aqueous PVP-I solution, has a significant benefit on SSI rate, particularly in clean and clean-contaminated wounds. No dose response effect was detected. With respect to incisional wound irrigation with saline, moderate to very low quality of evidence shows a significant effect on SSI rate when applied with force or using pulse pressure, but not with regular irrigation. There is no significant benefit for the use of antibiotic solutions for pIOWI or for the use of pIOWI in the abdomen or mediastinum.

Although recommendations from existing guidelines are conflicting (9, 10) and recent well-designed RCTs are lacking, up to 97% of the surgeons irrigate wounds in an effort to reduce the risk of SSI (6, 7). The most commonly used irrigation solution is saline followed by irrigation with aqueous PVP-I solutions or antibiotic solutions (6, 42, 43).

The efficacy and clinical safety of irrigation with these solutions has been under debate (11, 44). PVP-I is in varying concentrations rapidly effective against a broad spectrum of pathogens, Methicillin-resistant *Staphylococcus aureus* (MRSA) included (45, 46). However, some in vitro studies (47-49) have reported a negative effect of PVP-I on tissue regeneration and older case studies report serum iodine toxicity as a result of irrigation (50-52). However, these adverse effects could not be substantiated in clinical trials (29-35) (41). When considering antibiotics, the bactericidal effect of most agents requires a substantial interval of contact time. It is unlikely that pIOWI with antibiotic solutions is performed with sufficient time to achieve clinical efficacy, and anaphylactic reactions are reported (53). In addition, the misuse of antibiotics is considered to be a major driving force to the emergence of antimicrobial resistance (54-56). In contrast, resistance of organisms against antiseptics is suggested to be low, possibly due to their multiple pharmacological targets (57, 58). Wound irrigation using aqueous chlorhexidine (CHX) may be an alternative, when extrapolating the favourable results from alcohol-based CHX used for preoperative skin preparation, but clinical data are lacking. The results of aqueous 0.05% chlorhexidine gluconate as wound irrigation fluid in laboratory and animal studies are promising (59, 60).

Previous meta-analyses have assessed the effect of pIOWI but with serious limitations in their study selection impeding extrapolation to current clinical practice. Fournel et al. (61) have performed a systematic review of PVP-I in various applications and found a reduction of the incidence of SSI after aqueous PVP-I irrigation. Mueller et al. (8) have systematically assessed pIOWI with saline, PVP-I

and antibiotic solutions, and concluded that both PVP-I and antibiotic irrigation where effective in the reduction of SSI. However, both these reviews have included studies investigating IOWI as therapeutic measure for existing infections rather than as a preventive measure, and studies investigating IOWI while current standards of systemic antibiotic prophylaxis were not met. Fournel et al. (61) conducted a subgroup analysis of studies with standard systemic antibiotic prophylaxis but left relevant studies out (29, 30, 35). Mueller et al. has included PVP-I powder (spray) application among IOWI studies using an irrigation solution, but the mechanical effect of removal and dilution of the bacterial load is not achieved by powder application. Present systematic review specifically investigates the prophylactic effect of IOWI on the incidence of SSI against the background of current standard of care.

The limitations of the present study are generally allocated to the individual studies. The individual sample sizes are small resulting in little power per study and a high risk of failing to detect a true effect (β or type-two error). By conducting a meta-analysis, the power is increased and the risk of failing to detect a true effect reduced. Published studies on pIOWI are mostly conducted in the 1980s, which may represent a limitation as infection prevention and control measures have changed substantially since that period. Similarly, standards for the conduct and reporting of clinical trials have changed resulting in a stringent assessment of the quality of evidence. Strict inclusion criteria has limited the total of identified studies to 21 RCTs. Variation is seen in definition of SSI and follow up duration (appendix B) as the widely accepted definition of the CDC was first published in 1999 (15). Therefore, SSIs may be over-

or underreported. And finally, the exposure times and application methods were heterogeneous.

In absence of a proven effect of antibiotic irrigation and based on the risk of emerging antimicrobial resistance associated with the unnecessary use of antibiotics, irrigation with antibiotic solution should be avoided. Low quality evidence suggests benefit from incisional wound irrigation with aqueous povidone iodine. New high quality RCTs are needed but might not have priority considering the relatively large effect of prophylactic incisional wound irrigation using aqueous povidone iodine. A combined approach of several interventions to reduce SSIs may be more favourable since it has become apparent that a bundle approach has been successful in some studies (62-64).

Author Disclosure Statement

S.W. de Jonge, Q.J.J. Boldingh, J.S. Solomkin, B. Allegranzi and M. Egger declare no conflict of interest.

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Figure Legend

Figure 1: PRISMA flow chart of the systematic review

Figure 2a: Forrest plot of incisional wound irrigation with aqueous povidone-iodine vs. saline irrigation

Figure 2b: Forrest plot of incisional wound irrigation with aqueous povidone-iodine vs. saline irrigation stratified by wound contamination

Figure 2c: Forrest plot of incisional wound irrigation with aqueous povidone-iodine vs. saline irrigation stratified by povidone-iodine solution.

Figure 3: Forrest plot of incisional wound irrigation with antibiotic vs. saline irrigation, or no irrigation.

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Figure 1. PRISMA flow chart of the systematic review

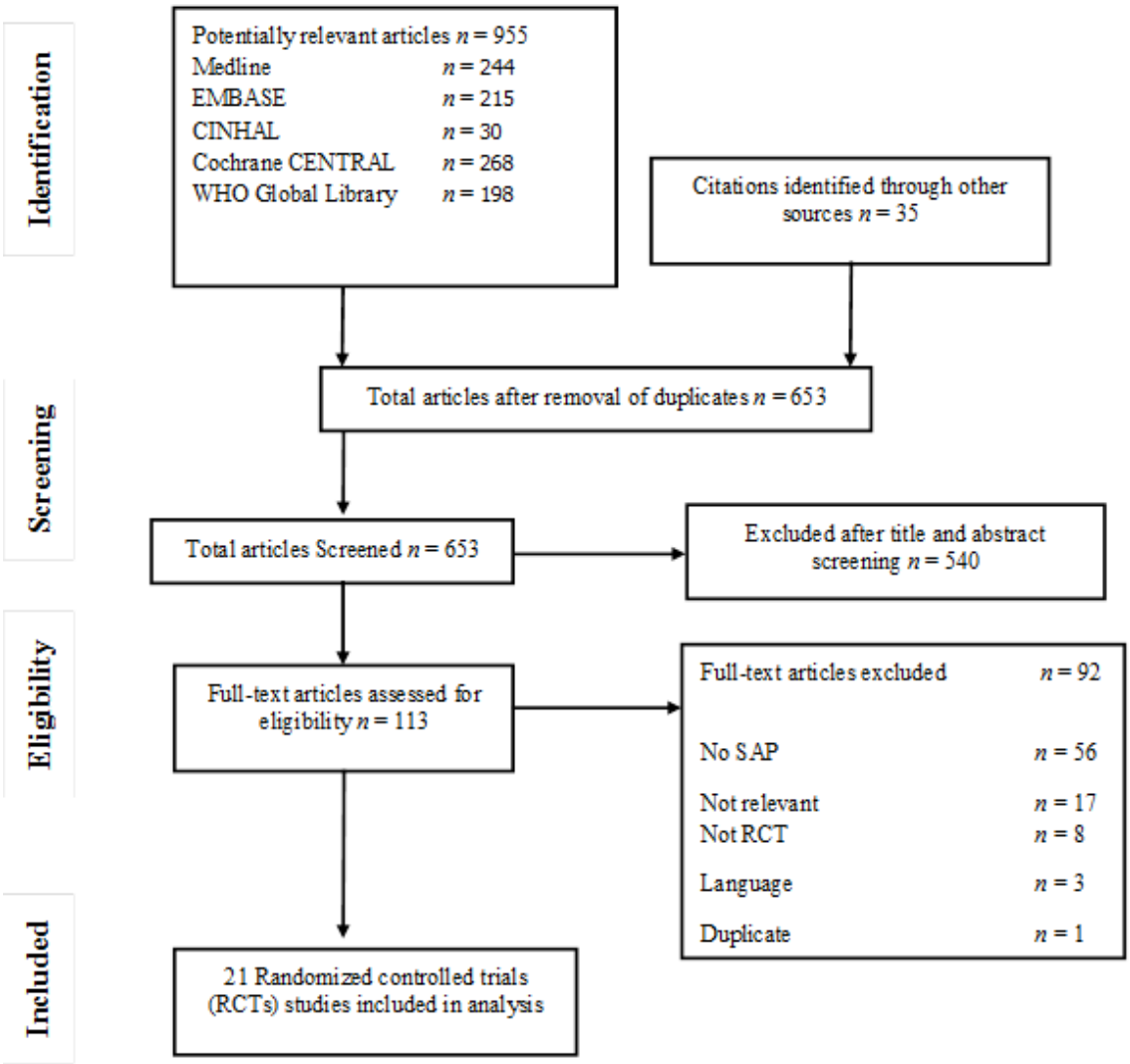

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Figure 2a

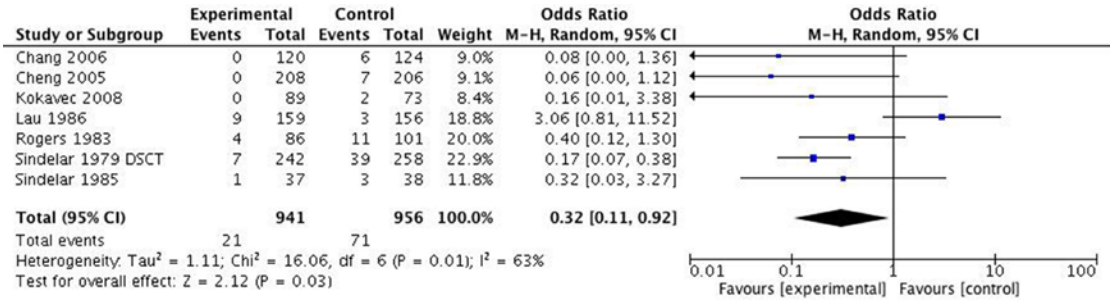

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Figure 2b

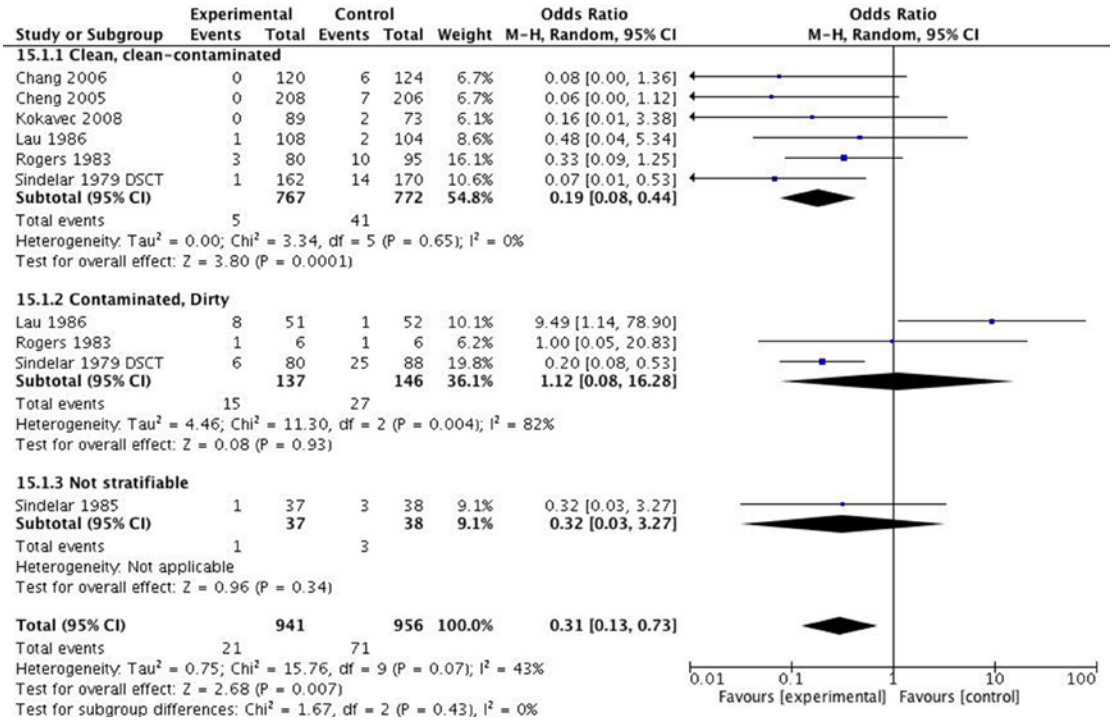

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Figure 2c

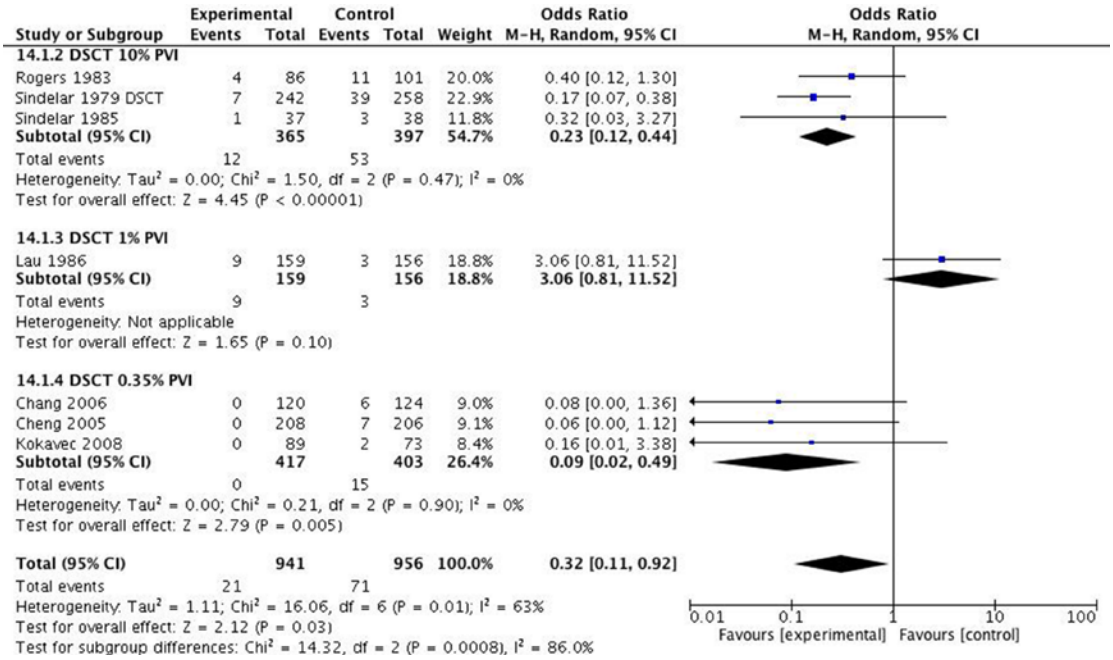

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Figure 3

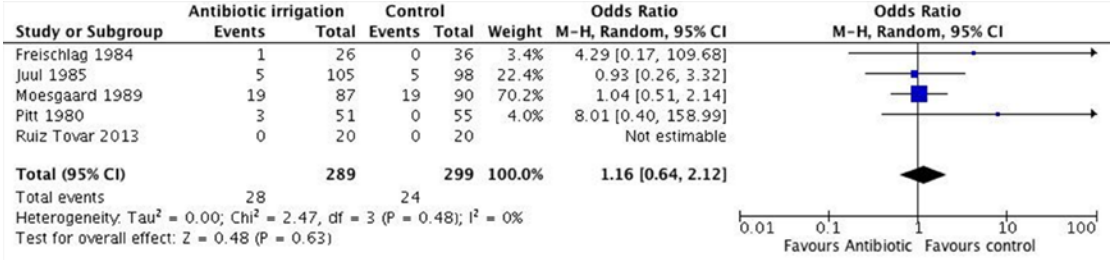

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Table 1. Explanatory table of definitions used

Prophylactic intraoperative wound irrigation (pIOWI)	The flow of a solution across the surface of an open wound to achieve wound hydration. It physically removes and dilutes body fluids, bacteria and cellular debris and additionally has a bactericidal effect when additives as antibiotics or antiseptic agents are used
Intraoperative wound irrigation as therapeutic intervention	CDC Wound class IV was considered a pre-existent infection; irrigation field was considered to be therapeutic not prophylactic
Intraoperative wound irrigation as prophylactic intervention	CDC wound class I-III was considered potentially contaminated; irrigation was considered to be prophylactic Irrigation of the newly made incisional wound was always considered prophylactic, regardless of the wound classification, as the incisional wound did not exist prior to the procedure and pre-existent wound infection was impossible.
Syringe pressure irrigation	Solution delivered with a syringe with an intravenous catheter applying force by hand.
Pulse pressure irrigation	Irrigation with the use of a mechanical device that delivers pulsatile saline irrigation.
US Centers for Disease Control and Prevention (CDC) wound classification	**Class I/Clean:** An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria. **Class II/Clean-Contaminated:** An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered. **Class III/Contaminated:** Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category. **Class IV/Dirty-Infected:** Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

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Table 2: summary evidence table

Study	Type of surgery	Irrigation surface	Intervention	Control	Follow-up	Primary outcome	Results
Tanaka 2015[18]	Elective liver resection	PC	1000-3000mL warm sterile saline solution directed at the dissected area	No irrigation	28 days	Incisional: clinically- apparent cellulitis, induration or purulent discharge from the closure site. Organ/space: radiological evidence of fluid collection necessitating drainage or antibiotic therapy	Total I: 21/96 C: 13/97 Incisional I:7/96 C: 6/97 Abscess I: 16/96 C: 7/97
Baker 1994[19]	Elective colorectal surgery	PC	250 mL taurolidine 2% in PVP-I 5%. Diluted in 250 mL saline solution followed by suction	500mL saline solution followed by suction	6 weeks	Spontaneous or incisional discharge from the wound with an infective organism identified on culture	Total: I: 17/150 C: 17/150 Incisional I: 17/150 C: 17/150 Abscess I: 2/150 C: 1/150
Freischlag 1984[20]	Elective biliary operations	IW & PC	Cefamandole nafate 0.4% solution (4 gm in 1000 mL normal saline solution)	No irrigation	30 days	Wound and intra-abdominal infections were defined by the spontaneous or surgical drainage of pus.	Total I: 1/26 C: 0/36 SSI I: 1/26 C: 0/36 Abscess I: 0/26 C: 0/36
Silverman 1986[21]	Elective or emergency trans-peritoneal intestinal surgery	PC	2 L 0.9% Sterile saline solution containing 2 g tetracycline	Sterile saline solution irrigation	6 weeks	Wound infection: Pus discharge from the wound. Intra-abdominal abscess: a mass palpable / identified radiologically plus spontaneous discharge /requiring surgical drainage.	Total I: 15/85 C: 25/74 SSI I :10/85 C: 24/74 Abscess I: 11/85 C: 10/74
Ruiz Tovar 2012[22]	Colorectal surgery	PC	Saline solution followed by a second lavage with gentamicin (240 mg) - clindamycin (600 mg) solution	Saline solution irrigation	30 days	Purulent discharge from the surgical wound confirmed by microbiological culture	SSI I: 2/51 C: 10/51 Incisional I: 2/51 C: 7/51 Abscess I: 0/51 C: 3/51
Al Ramahi 2006[23]	Caesarean sections	IW	50 mL normal saline solution	No irrigation	4 weeks	Discontinuation associated with purulent discharge and local tenderness, hotness and/or redness	SSI I: 11/104 C: 10/102

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Cervantes-Sanchez 2000[24]	Appendectomy	IW	300 mL saline solution delivered with a 20 mL syringe with a 1- gauge intravenous catheter applying the force of one hand at a distance of 2 cm from the wound	No irrigation	4 weeks	Clear collection of pus, which empties itself spontaneously or after incision	SSI I: 11/127 C: 39/156
Hargrove 2006[25]	Orthopaedics	IW	2 L pulse lavage saline	2 L saline via syringe	Discharge/ 30 days	CDC	SSI I: 9/164 C: 30/192
Nikfarjam 2014[26]	Laparotomy extending 2 hours	IW	Pressurized pulse lavage 15 psi Surgical irrigation device (Medline Industries, Mundelein, IL, USA)	Normal	30 days	CDC	SSI I:4/68 C: 12/62
Rogers 1983[27]	General surgery	IW	60-second irrigation with a PVP-I 10% solution	Saline solution	1 month	Purulent discharge.	SSI I: 04/86 C: 11/101
Sindelar 1979[28]	General surgery	IW	60-second irrigation with a PVP-I 10% solution	Saline solution	12 weeks	If any amount of pus was discharged/ serous drainage with bacterial growth	SSI I: 7/242 C: 39/258
Sindelar * 1985[29]	Intra-abdominal surgery	IW	IW: PVP-I 10%	Saline solution in PC Saline solution in IW	NR mean hospitalization > 3 weeks	NR	SSI I: 1/37 C: 3/38
Lau 1986[30]	Appendectomy	IW	10-minute irrigation with a PVP-I 1% solution	No irrigation	6 weeks	Clear collection of pus, which empties itself spontaneously or after incision	SSI I: 9/159 C: 3/156
Chang 2006[31]	Spine surgery	IW	180-second irrigation with PVP-I 0.35%, followed by copious irrigation with a normal saline solution	Irrigation with a copious saline solution	19.4 month	All deep infections were confirmed by laboratory parameters, including the erythrocyte sedimentation rate and level of C-reactive protein and a positive culture of biopsy	SSI I: 0/120 C: 6/124
Cheng 2005[32]	Spine surgery	IW	180-second irrigation with PVP-I 0.35%, followed by copious irrigation with a normal saline solution	Irrigation with a copious saline solution	15.5 month	Infection suspected when unusual pain, tenderness, erythema, induration, fever or wound drainage was observed. Confirmed by erythrocyte sedimentation rate, C-reactive protein and bacteriological cultures from the operative site or blood	SSI I: 0/ 208 C: 7/ 206
Kokavec 2008[33]	Orthopaedic	IW	PVP-I 0.35%	Saline solution	7.8 month	Pain, redness, swelling and increased temperature of the wound	SSI I: 0/89 C: 2/73
Juul 1985[34]	Elective colorectal surgery	IW	Ampicillin 1 g in 10 ml saline solution	No further prophylactic treatment	Until sutures removed	Accumulation of pus requiring surgical drainage	SSI I: 5/105 C: 5/98
Moesgaard 1989[35]	Intra-abdominal surgery	IW	Cefotaxime 2 g applied topically to the subcutaneous layer at the time of wound closure.	No irrigation	1 Month	Wound infection: accumulation of pus, draining spontaneously/ after opening the wound. IA: proven by	Total I: 19/87 C: 19/90 SSI I: 15/87

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						surgical drainage or by ultrasound-guided aspiration.	C: 14/90 Abscess I: 4/87 C: 5/90
Pitt 1980[36]	Vascular surgery	IW	Cephradine (1.0 g) dissolved in 25 ml of saline solution	Saline solution irrigation	4 weeks	Purulent material drained from the incision without evidence of prior ischemia of the skin edges.	SSI I: 3/51 C: 0/55
Ruiz Tovar 2013[37]	Lymph node dissection	IW	Normal saline solution plus Gentamicin 240 mg in 500 mL	Saline irrigation	NR	Wound infection	SSI I: 0/20 C: 0/20
Ko 1992[38]	Cardiac bypass surgery	MC	Irrigation with a PVP-I 0.5% solution	Irrigation with a saline solution	30 days	Mediastinitis. Pain, fever, erythema, drainage, sternal instability, tenderness on palpation and leukocytosis. Occasionally, mediastinal aspiration or CT was needed. Subcutaneous wound problems were not included	Mediastinal SSI I: 11/990 C: 6/990

CDC: Centers for Disease Control and Prevention; IW: incisional wound; PC: peritoneal cavity; NR: not reported; NA: not applicable; PVP-I: aqueous povidone-iodine; SSI: surgical site infection; I: intervention; C: control; LMW: low molecular weight

*** This study described peritoneal irrigation as well as incisional wound irrigation. However, intra-abdominal infections were not included in the analyses since infection of this field was pre-existent.**

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Table 3: Risk of bias table

Author	Sequence generation	Allocation concealment	Blinding of patients and staff	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Tanaka 2015[18]	Low	Low	High	High	Low	Low	Low
Baker 1994[19]	Low	Low	Low	Low	Low	Low	Low
Freischlag 1984[20]	Low	High	Unclear	Unclear	Low	Low	Low
Silverman 1986[21]	Low	Low	Unclear	Low	Low	High	Low
Ruiz Tovar 2012[22]	Low	Low	Unclear	Low	High	Low	Low
Al-Ramahi 2006[23]	High	High	High	High	Low	Low	Low
Cervantes-Sánchez 2000[24]	Low	Low	High	Low	Low	Low	Low
Hargrove 2006[25]	Unclear	Unclear	Unclear	Unclear	High	Low	Low
Nikfarjam 2014[26]	Low	Unclear	High	High	Low	Low	Low
Rogers 1983[27]	High	High	High	Unclear	Low	Low	Low
Sindelar 1979[28]	Unclear	Unclear	High	Unclear	Low	Low	Low
Sindelar 1985[29]	Unclear	Unclear	High	Unclear	Low	Low	Low
Lau 1986[30]	Unclear	Unclear	High	Low	Low	Low	Low
Chang 2006[31]	Low	Unclear	High	Low	Low	Low	Low
Cheng 2005[32]	Low	Unclear	High	Low	Low	Low	Low
Kokavec 2008[33]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Juul 1985[34]	Low	High	Unclear	Unclear	Low	Low	Low
Moesgaard 1989[35]	Unclear	High	High	Low	Low	Low	Low
Pitt 1980[36]	Unclear	Unclear	Unclear	Low	Low	Low	Low
Ruiz Tovar 2013[37]	Low	Low	Unclear	Unclear	Low	High	Low
Ko 1992[38]	High	High	Unclear	Unlcear	Low	Low	Low

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Appendix A: Search terms

MEDLINE	1. "surgical wound infection"[Mesh] OR surgical site infection*[tiab] OR SSI[tiab] OR SSIs[tiab] OR surgical wound infection*[tiab] OR surgical infection*[tiab] OR post-operative wound infection*[tiab] OR postoperative wound infection*[tiab] 2. irrigat*[tiab]) OR lavag*[tiab]) OR spray*[tiab]) OR soak*[tiab]) OR rins*[tiab] OR "therapeutic irrigation"[Mesh] 3. trial[ti]) OR randomly[tiab]) OR clinical trial as topic[mesh:noexp]) OR placebo[tiab]) OR randomized[tiab]) OR controlled clinical trial[pt]) OR randomized controlled trial[pt] 4. 1 AND 2 AND 3
EMBASE	1. exp surgical infection/ or (SSI or SSIs).ti,ab,kw. or ((surg* or postoperat* or post-operat*) adj3 infect*).ti,ab,kw 2. wound irrigation / or lavage/ or (irrigat* or lavag* or spray* or soak* or rins*).ti,ab,kw. 3. controlled clinical trial/ or randomized controlled trial/ or exp "clinical trial (topic)"/ or (randomly or randomized or placebo).ti,ab,kw. or trial.ti. 4. 1 AND 2 AND 3
COCHRANE REGISTER (CENTRAL)	1. MeSH descriptor: [surgical wound infection] explode all trees 2. SSI or SSIs:ti,ab,kw (word variations have been searched) 3. (surg* or postoperat* or post-operat*) near/3 infect*:ti,ab,kw (word variations have been searched) 4. 1 OR 2 OR 3 5. irrigat* or lavag* or spray* or soak* or rins*:ti,ab,kw (word variations have been searched) 6. 4 AND 5
CINAHL	1. (MH "surgical wound infection") OR (TI (surgical site infection* OR SSI OR SSIs OR surgical wound infection* OR surgical infection* OR post-operative wound infection* OR postoperative wound infection*) OR AB (surgical site infection* OR SSI OR SSIs OR surgical wound infection* OR surgical infection* OR post-operative wound infection* OR postoperative wound infection*)) 2. (MH "therapeutic irrigation") OR TI (irrigat* or lavag* or spray* or soak* or rins*) OR AB (irrigat* or lavag* or spray* or soak* or rins*) 3. (MH "randomized controlled trials") OR (MH "clinical trials+") OR TI trial OR (TI controll* AND trial*) OR AB (TI controll* AND trial*) OR (TI (randomly OR placebo OR randomi?ed) OR AB (randomly OR placebo OR randomi?ed)) 4. S1 AND S2 AND S3
WHO Global Regional Medical Databases	1. (SSI) 2. (surgical site infection) 3. (surgical site infections) 4. (wound infection) 5. (wound infections) 6. (postoperative wound infection) 7. (irrigation) 8. (lavage)
Abbreviations: ti: title; ab: abstract: kw: keywords.	

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Appendix B: Evidence table

Reference	Design, scope, participants (no)	Type of surgery	CDC wound classification	Irrigation surface	Intervention	Control	Follow-up	Primary outcome	Results	Adverse events
Tanaka 2015 [18]	RCT single centre 193	Elective liver resection without reconstruction of bile duct or small intestine	II	PC	Irrigation with 1000-3000 mL warm sterile saline solution directed at the dissected area. Both groups used wound washout with a warm sterile saline solution	No irrigation	28 days	Incisional: clinically-apparent cellulitis, induration or purulent discharge from the closure site. Organ/space: radiological evidence of fluid collection necessitating drainage or antibiotic therapy.	SSI I: 21/96 C: 13/97 Incisional: 7/96 C: 6/97 Abscess I: 16/96 C: 7/97	NR
Baker 1994 [19]	RCT single centre 330	Elective colorectal surgery	II	PC	250 mL taurolidine 2% in PVI 5%. Diluted in 250 mL saline solution followed by suction	250 mL saline solution Diluted in 250 mL saline solution followed by suction	6 weeks	Spontaneous or incisional discharge from the wound with an infective organism identified on culture.	Total: I: 17/150 C: 17/150 Abscess I: 2/150 C: 1/150 Incisional I: 17/150 C: 17/150	NR
Freischlag 1984 [20]	RCT single centre 62	Elective billary operations	II-III	IW & PC	Cefamandole nafate 0.4% solution (4 gm in 1000 mL normal saline solution)	No irrigation	30 days	Wound and intra-abdominal infections were defined by the spontaneous or surgical drainage	SSI I: 1/26 C: 0/36 Abscess	NR

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								of pus.	I: 0/26 C: 0/36 Total I: 1/26 C: 0/36	
Silverman 1986 [21]	RCT single centre 159	Elective or emergency trans-peritoneal intestinal surgery	II-III	PC	2 L 0.9% Sterile saline solution containing 2 g tetracycline	Sterile saline solution irrigation	6 weeks	Wound infection: Pus discharge from the wound. IA abscess: a mass palpable / identified radiologically plus spontaneous discharge /requiring surgical drainage.	SSI I :10/85 C: 24/74 Abscess I: 11/85 C: 10/74 Total I: 15/85 C: 25/74	NR
Ruiz Tovar 2012 [22]	RCT single centre 103	Colorectal surgery	II-III	PC	Saline solution followed by a second lavage with gentamicin (240 mg) - clindamycin (600 mg) solution	Saline solution irrigation	30 days	Purulent discharge from the surgical wound confirmed by microbiological culture.	SSI I: 2/51 C: 10/51 Incisional I: 2/51 C: 7/51 Abscess I: 0/51 C: 3/51	NR
Al Ramahi 2006 [23]	RCT single centre 206	Caesarean section	II	IW	50 mL normal saline solution	No wound irrigation	4 weeks	Discontinuation associated with purulent discharge and local tenderness, hotness and/or redness	SSI I: 11/104 C: 10/102	NR

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Cervantes-Sanchez 2000 [24]	RCT single centre 283	Appendectomy	II-IV	IW	300 mL saline solution delivered with a 20 mL syringe with a 1- gauge intravenous catheter applying the force of one hand at a distance of 2 cm from the wound	No irrigation	4 weeks	Clear collection of pus, which empties itself spontaneously or after incision,	SSI I: 11/127 C: 39/156	NR
Hargrove 2006 [25]	RCT multicentre 356	Orthopaedics	I	IW	2 L pulse lavage saline	2 L saline via syringe	Discharge / 30 days	CDC	SSI I: 9/164 C: 30/192	
Nikfarjam 2014 [26]	RCT multicentre 128	Laparotomy extending 2 hours (hepato-pancreato-biliary)	II-III	IW Both groups: lavage of the PC with a warm saline solution	Pressurized pulse lavage 15 psi Surgilav irrigation device (Medline Industries, Mundelein, IL, USA)	Normal	30 days	CDC	SSI I:4/68 C: 12/62	NR
Rogers 1983 [27]	RCT single centre 187	General surgery	I-IV differentiated	IW	60-second irrigation with a PVI 10% solution	Saline solution	1 month	Purulent discharge.	SSI I: 04/86 C: 11/101	No AE
Sindelar 1979 [28]	RCT single centre 500	Abdominal, gastrointestinal, oncologic, vascular, head and neck, thoracic, genitourinary, trauma	I-IV	IW	60-second irrigation with a PVI 10% solution	Saline	12 weeks	If any amount of pus was discharged/ serous drainage with bacterial growth.	SSI I: 7/242 C: 39/258	No AE

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Sindelar 1985 [29]	RCT single centre 75	Intra-abdominal surgical procedures	III-IV	PC & IW	3 x 30-60 second irrigation with sterile LMW PVI 1% solution followed by suction (last irrigation immediately prior to closure.DSC: PVI 10%	Saline solution in PC Saline solution in IW	NR mean hospitalization > 3 weeks	NR	SSI I: 1/37 C: 3/38 Abscess I: 1/37 C: 7/38 Total I: 2/37 C: 10/38	No AE (brief iodine elevation but no signs of toxicity)
Lau 1986 [30]	RCT single centre 315	Appendectomy	II-IV	IW	10-minute irrigation with a PVI 1% solution	No irrigation	6 weeks	Clear collection of pus, which empties itself spontaneously or after incision	SSI I: 9/159 C: 3/156	NR
Chang 2006 [31]	RC Single centre 244	Spine	I	IW	180-second irrigation with PVI 0.35%, followed by copious irrigation with a normal saline solution	Irrigation with a copious saline solution	19.4 month	All deep infections were confirmed by laboratory parameters, including the erythrocyte sedimentation rate and level of C-reactive protein and a positive culture of biopsy.	SSI I: 0/120 C: 6/124	NR; no difference on fusion rate, function or pain
Cheng 2005 [32]	RCT single centre 414	Spine surgery	I	IW	180-second irrigation with PVI 0.35%, followed by copious irrigation with a normal saline solution	Irrigation with a copious saline solution	15.5 month	Infection was suspected when unusual pain, tenderness, erythema, induration, fever or wound drainage was observed. Confirmed by erythrocyte sedimentation rate, C-reactive protein and bacteriological cultures from the operative	SSI I: 0/208 C: 7/206	No AE No effect on union time or quality of bony fusion was noted.

								site or blood.		No allergy
Kokavec 2008 [33]	RCT single centre 162	Orthopaedic	I	IW	PVI 0.35%	Saline	7.8 month	Pain, redness, swelling and increased temperature of the wound.	SSI I: 0/89 C: 2/73	NR
Juul 1985 [34]	RCT single centre 203	Elective colonic and rectal surgery	II-III	IW	Ampicillin 1 g in 10 ml saline solution	No further prophylactic treatment	Until sutures were removed	Accumulation of pus requiring surgical drainage,	SSI I: 5/105 C: 5/98	No AE
Moesgaard 1989 [35]	RCT single centre 1989	Intra-abdominal operation	IV	IW	Cefotaxime 2 g applied topically to the subcutaneous layer at the time of wound closure.	No irrigation	1 Month	Wound infection: accumulation of pus, draining spontaneously/ after opening the wound. IA: proven by surgical drainage or by ultrasound-guided aspiration.	SSI I: 15/87 C: 14/90 Abscess I: 4/87 C: 5/90 Total I: 19/87 C: 19/90	NR
Pitt 1980 [36]	RCT ingle centre 106	Vascular surgery	I	IW	Cephradine (1.0 g) dissolved in 25 ml of saline solution	Saline solution irrigation	4 weeks	Purulent material drained from the incision without evidence of prior ischemia of the skin edges.	SSI I: 3/51 C: 0/55	NR
Ruiz Tovar 2013 [37]	RCT single centre 40	Lymph node dissection	I	IW	Normal saline solution plus Gentamicin 240 mg in 500 mL	**Saline irrigation**	NR	Wound infection.	SSI I: 0/20 C: 0/20	NR
Ko 1992 [38]	RCT single cente 1980	Cardiac bypass surgery	I	MC Subcutaneous wound	Irrigation with a PVI 0.5% solution	Irrigation with a saline solution	30 days	Mediastinitis. Pain, fever, erythema, drainage, sternal instability, tenderness on palpation and leukocytosis.	Mediastinal SSI I: 11/990	NR

				was copiously irrigated before skin closure				Occasionally, mediastinal aspiration or CT was needed. Subcutaneous wound problems were not included	C: 6/990	

CDC: Centers for Disease Control and Prevention; IW: incisional wound; PC: peritoneal cavity; NR: not reported; NA: not applicable; PVI: povidone-iodine; AE: adverse event; SSI: surgical site infection; I: intervention; C: control; RCT: randomized controlled trial; LMW: low molecular weight;

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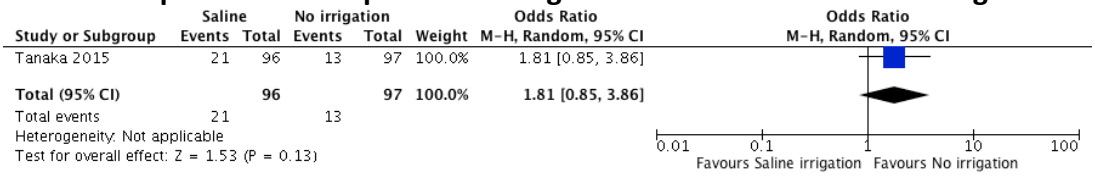
Appendix D. All comparisons

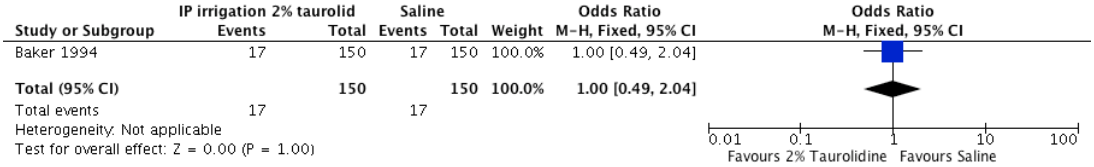
Comparison 1: Intraperitoneal irrigation: Saline solution *vs*. no irrigation



*Meta-analysis of one study does not comprise actual pooled data, but is included for purposes of illustration.

Funnelplot not applicable

Comparison 2: Intraperitoneal irrigation: Taurolidine 2% *vs*. saline solution*



*Meta-analysis of one study does not comprise actual pooled data, but is included for purposes of illustration.

Funnelplot not applicable

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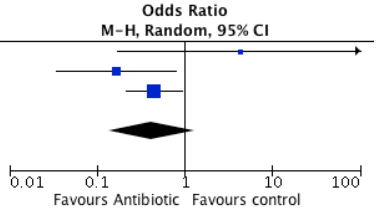
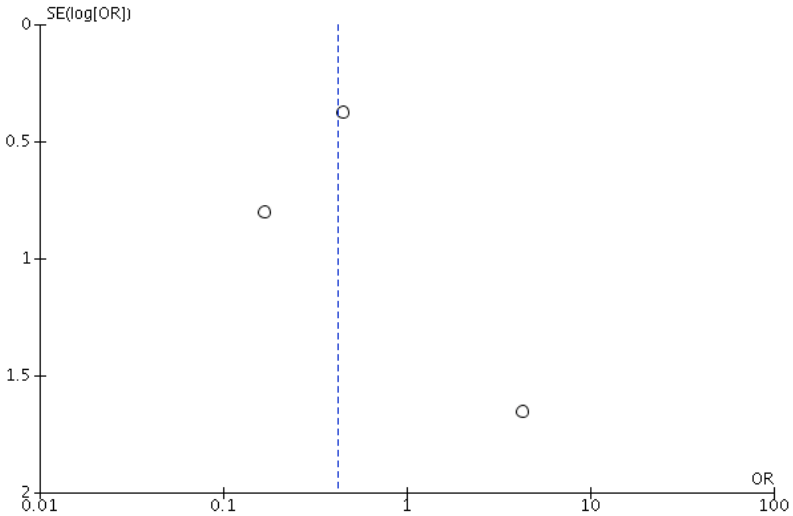
Comparison 3: Intraperitoneal irrigation: Antibiotic *vs.* saline or no irrigation

Study or Subgroup	Antibiotic irrigation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Freischlag 1984	1	26	0	36	10.4%	4.29 [0.17, 109.68]
Ruiz Tovar 2012	2	51	10	51	30.9%	0.17 [0.03, 0.81]
Silverman 1986	15	85	24	74	58.6%	0.45 [0.21, 0.94]
Total (95% CI)		**162**		**161**	**100.0%**	**0.42 [0.14, 1.29]**
Total events	18		34			

Heterogeneity: Tau² = 0.42; Chi² = 3.31, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 1.52 (P = 0.13)



Funnelplot:



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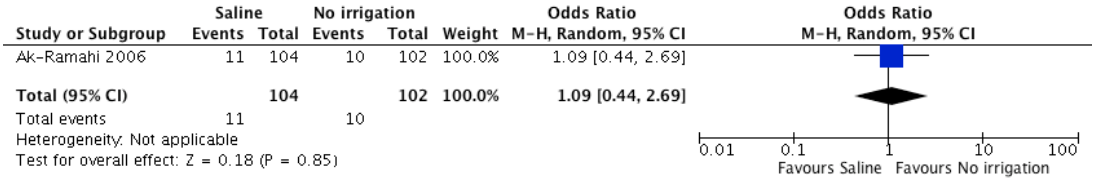
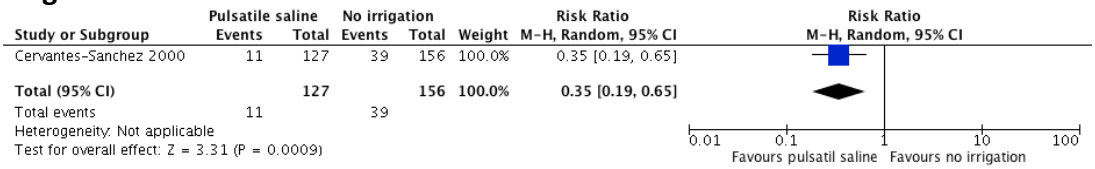
Comparison 4: Incisional wound irrigation: Saline solution *vs.* no irrigation



*Meta-analysis of one study does not comprise actual pooled data, but is included for purposes of illustration

Funnelplot not applicable

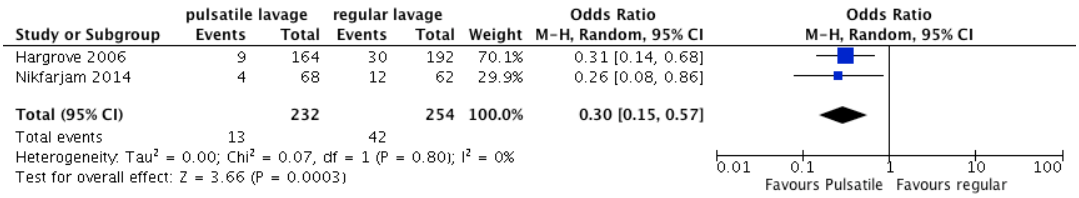
Comparison 5: Incisional wound irrigation: Syringe pressure saline *vs.* no irrigation*



*Meta-analysis of one study does not comprise actual pooled data, but is included for purposes of illustration

Funnelplot not applicable

Comparison 6: Incisional wound irrigation: Pulse pressure irrigation



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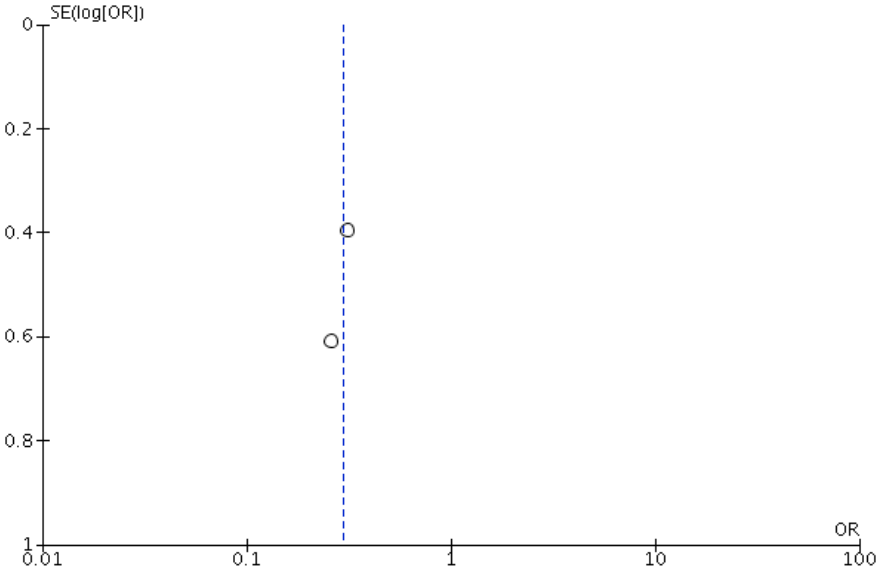
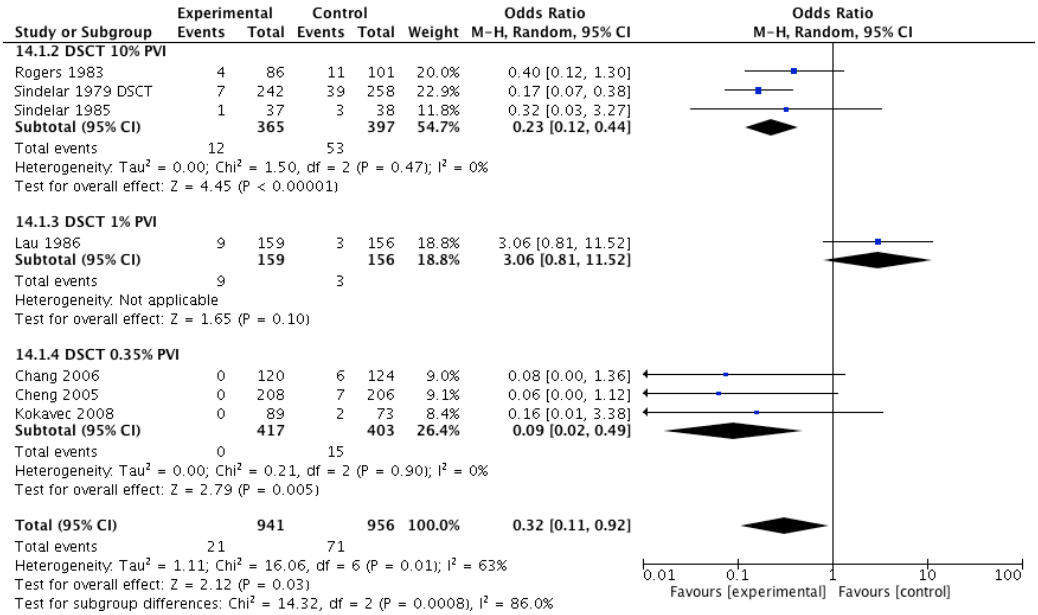
Funnelplot:



Comparison 7: Incisional wound irrigation: Aqueous povidone-iodine *vs*. saline irrigation

- Stratified by povidone-iodine solution (7a)



- Stratified by wound contamination class (7b)

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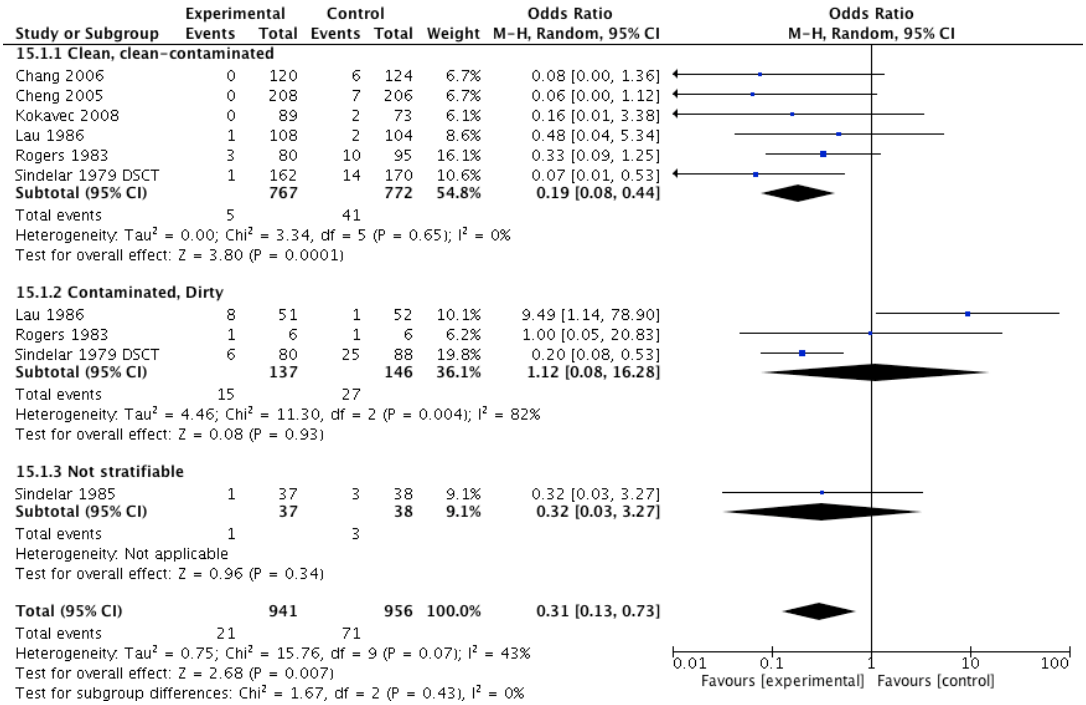

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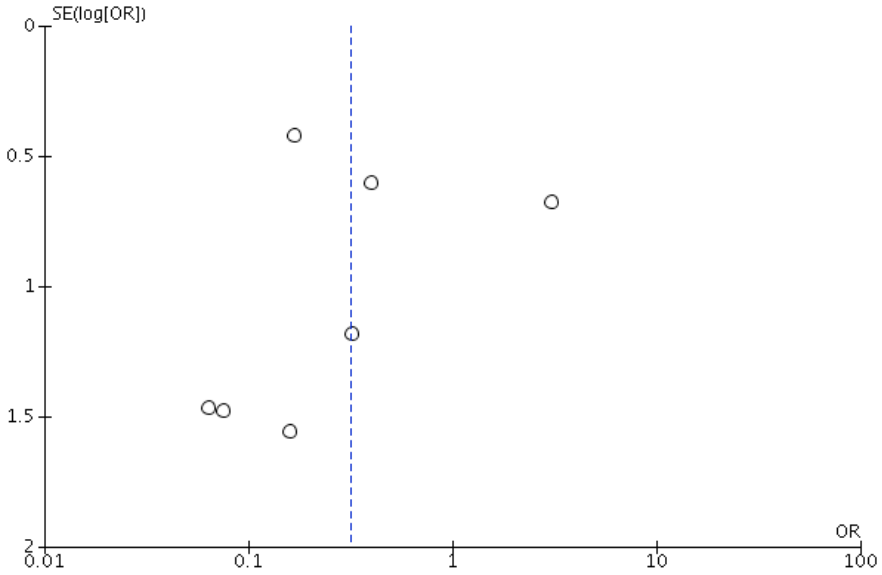

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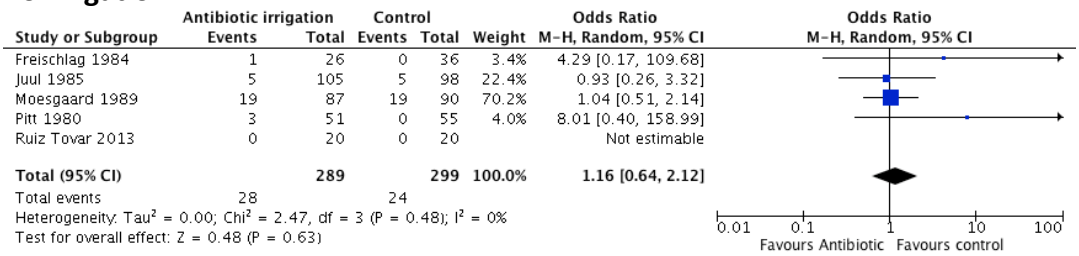
Comparison 8: Incisional wound irrigation: antibiotic *vs.* saline irrigation, or no irrigation



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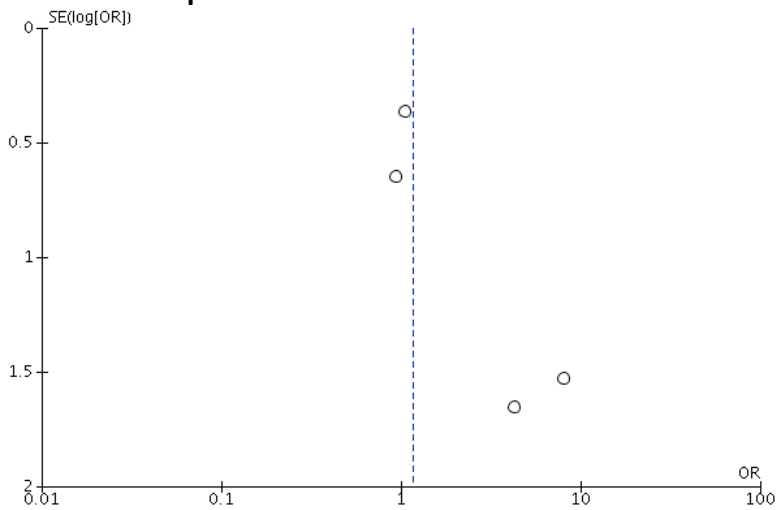
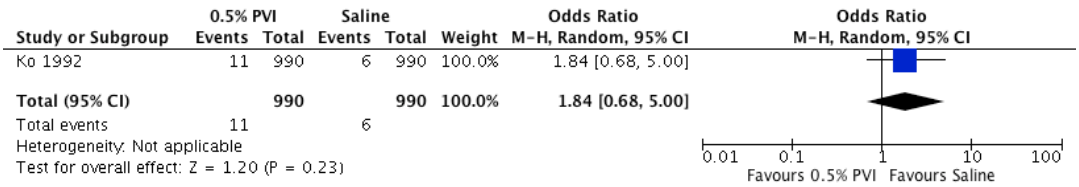


Comparison 9: Mediastinal irrigation: povidone-iodine 0.5% *vs*. saline irrigation*



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M-H: *Mantel*-Haenszel (test); CI: confidence interval

Funnelplot not applicable